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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/757,555	01/09/2001	Levon Michael Khachigian	273402002020	9700

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EXAMINER	
EPPS, JANET L	

ART UNIT	PAPER NUMBER
1635	10

DATE MAILED: 04/23/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/757,555	KHACHIGIAN, LEVON MICHAEL	
	Examiner	Art Unit	
	Janet Epps	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-3 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-3 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 09 January 2001 is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/142,779 .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Drawings

2. In order to avoid abandonment, the drawing informalities noted in the PTO-948 attached to Paper No. 4, mailed on 7-31-01, must now be corrected. Correction can only be effected in the manner set forth in the above noted paper.

Sequence Listing

3. The sequence listing submitted 1-31-02 is technically sound and has been entered into the pending nucleic acid sequence database of the USPTO-STIC facility.

Response to Amendment

4. Claims 1-2 remain rejected under 35 U.S.C. 102(b) as being anticipated by Hu et al., for the reasons of record set forth in the Official Action mailed July 31, 2001. Applicant's arguments filed 1-31-2002 have been fully considered but they are not persuasive.

Applicants traverse the instant rejection on the grounds that the Hu et al. reference exclusively deals with the growth of central nervous system (astrocyte) cells, and the observations made by Hu, *et al.* relate specifically to modulation of astrocyte proliferation. However, contrary to Applicants assertions, the Hu et al. reference teaches the regulation of Egr-1 (Tis –8) in a rat glioma cell line (page 1825, paragraph 3, Figure 7), wherein said glioma cells are a type of neoplasia cells as recited in the instant claims.

5. Applicant's arguments with respect to claims 1-3 are rejected over Muthukkumar et al. have been considered but are moot in view of the Examiner's withdrawal of this rejection and the following new ground(s) of rejection.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mendelsohn et al.

The instant claims read on a method of screening for compounds that inhibit proliferation of cells selected from the group consisting of vascular cells and neoplasia cells, the method comprising determining the ability of a putative compound to inhibit induction of Egr-1, decrease expression of Egr-1 or decrease the nuclear accumulation or activity of the Egr-1 gene product wherein the method is performed *in vitro*, and further wherein the vascular cells are selected from the group consisting of smooth muscle cells and endothelial cells.

Mendelsohn et al. provides screening methods that can be used to identify vasoprotective agents, which inhibit vascular smooth muscle cell activation and/or proliferation or enhance vascular endothelial cell activation and/or proliferation or activate estrogen responsive genes in vascular cells. One type of screening assay described in this reference involves examining the effect of a candidate vasoproctective agent on reporter constructs to indirectly monitor the effect of the agent on the proliferation and/or activation of vascular cells and to monitor the effect of an

agent on the expression of an estrogen responsive gene. In one specific embodiment of this invention, Mendelsohnn et al. describe the use of a reporter construct comprising an estrogen receptor responsive gene, wherein preferred vasoprotective agents are identified by their ability to influence the expression of an estrogen responsive gene. For example, in each of the following cases the format ("+" or "-") describes the preferred response in vascular endothelial cells / preferred response in vascular smooth muscle cells: prostaglandin cyclooxygenase (+/+), prostaglandin synthase (+/+), nitric oxide synthase (constitutive or calcium-dependent) (+/+), collagen (-/-), elastin (-/-), c-fos (+/-), progesterone receptor (+/+), vascular endothelial growth factor (+/+), epidermal growth factor receptor (-/-), interleukin-6 (+/+), neu (-/-), egr-1 (-/-), estrogen receptor (+/+), heat shock protein 27 (+/-), vascular adhesion molecules (-/-), vascular smooth muscle cell calcium channels (-/-), ryanodine receptor (-/-), FLT4 receptor tyrosine kinase (+/-), fibroblast growth factor receptor (-/-), and inducible nitric oxide synthase (+/+). Therefore, (+/+) refers to wherein indicates that the preferred agents increase expression of that gene (or a reporter operably linked to the upstream control region of that gene in the indicated cell type), and (-/-) refers to the ability of the preferred agent to inhibit or decrease expression of said gene or reporter gene (col. 11, lines 37-54).

Mendelsohnn et al. does not explicitly describe a method of screening for compounds that inhibit proliferation of cells selected from vascular smooth muscle cells or endothelial cells, wherein the method specifically comprises determining the ability of a putative compound to inhibit induction of egr-1.

Absent evidence to the contrary, one of ordinary skill in the art at the time of filing of the instant application seeking alternative means for identifying potential vasoprotective agents, and

in view of the teachings of Mendelsohnn et al., would have been motivated to design a reporter construct comprising either the egr-1 gene as a reporter gene or comprising the upstream regulatory sequence of egr-1 in combination with another reporter gene, to be used in a method for identifying compounds that inhibit proliferation of cells by determining the ability of said compound to inhibit or decrease the expression of the egr-1 reporter construct. It would have been obvious to one of ordinary skill in the art to modify the teachings of Mendelsohnn et al. to design the methods of the claimed invention since Mendelsohnn et al. clearly teach that "any gene which is responsive to an estrogen receptor can serve as the basis for a reporter construct (col. 11, lines 22-23)," wherein said reporter constructs are "used to indirectly monitor the effect of an agent on the proliferation and/or activation of vascular cells and to monitor the effect of an agent on the expression of an estrogen responsive gene (col. 11, lines 12-15)." Mendelsohnn et al. goes on to describe vascular genes of interest to be used in said reporter constructs, wherein the list of vascular genes comprises the "egr-1" gene (col. 11, lines 29). Additionally, Mendelsohnn et al. specifically teaches that the expected effect of the potential vasoproctective agent on the expression of egr-1 is a decrease (-/-) in expression of egr-1 in both vascular smooth muscle cells and vascular endothelial cells (col. 11, lines 46-54).

Therefore, the invention as a whole would have been prima facie obvious over Mendelsohnn et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L Epps, Ph.D. whose telephone number is 703-308-8883. The examiner can normally be reached on M-T, Thurs-Friday 8:30AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703)-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-746-5143 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Janet L Epps, Ph.D.
Examiner
Art Unit 1635

JLE
April 20, 2002

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
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